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Development and evaluation of self micro emulsifying drug delivery system of Itraconazole

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ABSTRACT

The aim of the present study was to formulate and evaluate self micro emulsifying drug delivery system to enhance the solubility of the BCS class II drug, i.e. itraconazole. SMEDDS of the model drug were prepared using castor oil and benzyl alcohol as oil phase, tween 80 as surfactant and poly ethylene glycol 400 and ethanol as co-solvents. The prepared SMEDDS were characterized by SEM and zeta potential. SMEDDS were evaluated for globule size, stability studies, dispersibility test and *in vitro* drug release. SEM photograph showed that globules were smooth and spherical in shape. The particle size and zeta potential of prepared formulation was found to be between 8-16 µm and -11.5 to -55.6 respectively. Stability of itraconazole drug was found to depending on the amount of castor oil present in the formulation. As concentration of castor oil in the formulation increases, so the stability. *In vitro* drug release of the formulations was carried out in pH 1.2 buffer for 2 hours. Formulation F6 showed 98.50% drug release at the end of 2 hours. It was concluded that the SMEDDS prepared seem to promising carriers for enhancing the bioavailability and the solubility of poorly water soluble drug.

Keywords: SMEDDS, Itraconazole, Castor oil, pH 1.2 buffer.

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INTRODUCTION

The hydrophobicity or the poor water solubility of the drug results in low bioavailability of the drug which in turn reduces the therapeutic action of the drug. To overcome this problem lipid based formulations have been developed. Mostly the new drugs show less water solubility which leads to poor bioavailability, high intra- and inter- subject variability and lack of dose proportionality. Several approaches are being made for the improving the dissolution rate of these drugs. Among these Self emulsifying drug delivery System have shown a great promise in improving the bioavailability of poorly water soluble drugs.

Self emulsifying drug delivery system is a novel drug delivery system in which the drug is incorporated into oil, surfactant and co-surfactant such that the drug solubility is enhanced and so is its bioavailability. The process of self emulsification is limited to a particular pair of oil and surfactant, concentration of surfactant, the ratio of oil-surfactant, as well as the temperature that the self emulsification takes place .following the self-dispersion, fast drug distribution throughout the GIT happens in the shape of fine droplets,. The dissolution is improved by the large surface areas. Solubilization of The emulsion globules in the GIT then happens by the bile fluids. The surfactant existence leads to the enhancement of the absorption because of the activated permeation changes in the membrane. The formed droplets are either charged positively or negatively, the lining of the mucosa has a negative charge, it was detected that particles which are positively charged penetrated deeper into the ileum .anionic emulsion has less bio-availbity than cationic emulsions .Both self emulsifying drug delivery system and self micro emulsifying drug delivery system are stable preparations that help in the improvement of the drug dissolution due to the high surface area on dispersion. The emulsified form itself is readily absorbable which assures the movement of drugs that are poorly soluble into the blood more rapidly. Many studies have noted the applications and uses of self emulsifying drug delivery system in delivering and targeting lipophilic drugs such as coenzyme Q1013, vitamin E14, halofantrine15 and cyclosporine A16. Upon per oral administration, these systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility. [1]

Based on the globule size of the emulsion formed, SEDDS can be self microemulsifying drug delivery system (SMEDDS) and self nano emulsifying drug delivery system (SNEDDS). SMEDDS are clear, transparent micro emulsions with droplet size ranging between 100 to 250µm. Whereas SNEDDS, which is new member to the SEDDS family, form nanoemulsions upon dispersion in water of droplet size less than 100nm.

This present study involves the preparation of self micro emulsifying drug delivery system. Itraconazole was used as model drug. Itraconazole is used for the treatment of fungal diseases. Itraconazole show least aqueous solubility and has low bioavailability. Hence this drug was incorporated into SMEDDS as fine droplets which will enhance the solubility in GIT and thus its bioavailability. [1]

MATERIALS AND METHOD

Itraconazole was procured from Metrochem API private limited, Hyderabad, India. Castor oil was purchased from Avonchem, UK, Tween and PEG 400 were purchased from Scharlab S L Spain. All other ingredients used were of analytical grades.

Preparation of self emulsifying drug delivery system by emulsion formation.

Itraconazole was dissolved completely in benzyl alcohol and then mixed with castor oil small increment with continuous stirring. The system of the surfactant was made by individually mixing the required surfactant and co-surfactant in their specific ratios. Itraconazole which that has oil solution was added in the surfactant system solution with regular stirring using magnetic stirrer. Keep on stirring until the homogenous mixture forms. lastly the mixture was preserved at room temperature. Itraconazole loaded SMEDDS formulations (F1, F2, F3, F4, F5, F6 and F7) were imposed to more characterization. Detailed compositions of SMEDDS formulations are found in table 1. [2]

Table 1: Formulation chart

Formulation	Drug(mg)	Benzyl alcohol(ml)	Castor oil(ml)	PEG400 (ml)	Ethanol (ml)	Tween 80(ml)
F1	100	1.00	5.00	2.00	2.00	8.00
F2	100	1.00	3.00	1.30	1.30	5.30
F3	100	1.00	4.00	1.67	1.67	6.60
F4	100	1.00	2.50	1.10	1.10	4.60
F5	100	1.00	2.00	1.00	1.00	4.00
F6	100	1.00	6.00	2.30	2.30	9.20
F7	100	1.00	6.50	2.50	2.50	10.0

Characterisation of SMEDDS:

Zeta potential:

Zeta potential is used for the identification of the charges on globules. Zeta potential helps in predicting the stability and flocculation effect in emulsion system. If the zeta potential is less than a certain level, aggregation of colloid will take place due to the forces of attraction. Conversaly a zeta with high potential maintains a stable system. [3] light scattering methods are used for the measurment of the zeta potential by an instrument called zetasizer. The instrument helps in the

measurment of the zeta potential to optimise shelf life and stability and speed up the development of the formulation. The zeta potential of the dispersions is measured by the instrument according to the Helmholtz- Smoluchowski equation.

$$U = \frac{\varepsilon \xi Ex}{\mu}$$

Where, U is the electrophoretic velocity, E is the permittivity, ξ is the zeta potential, E_x is the axial electric field, μ is the viscosity.

Range of zeta potential along with the behaviour of emulsion is shown in table 2.

Table 2: Zeta potential range and stability behaviour of emulsion [4]

Zeta potential (mV)	Stability behaviour of emulsion
0 to ±5	Rapid coagulation or flocculation
10 to ±30	Incipient instabilty
40 to ±60	Good stabilty
> 61	Excellent stabilty

Scanning Electron Microscope (SEM):

surface characteristics of the prepared pH sensitive globules and Morphology were determined using SEM (SURA LAB, Hyderabad). The photographs were checked to get the morphological characteristics and for the golbule spherical nature to be formed by SMEDDS.[3]

Evaluation of SMEDDS:

Solubility:

Solubility of itraconazole was checked in various oils, cosurfactants and surfactants by the addition of extra drug amount (app. 500 mg) in a screw capped vials containing 5ml of vehicle. The mixture was heated for 50 ºC in a water bath to facilitate solubility using magnetic stirrer. Mixtures were shaken with mixers at 40 ºC for 48 hrs. After reaching the equilibrium the vials were being centrifuged for 15 min at maximum rpm and insoluble excess drug was filtered using membrane filter.

Globule size: the size of the Globule is a very important factor in self emulsification performance because it helps in the determination of the rate and extends of the release of drug as well as absorption. It was measured by Microscopical method.[5]

Eye piece micrometer was calibrated using stage micrometer and calibration factor was calculated. 1ml of the prepared itraconazole SMEDDS was diluted to 100 ml with distilled water and a milky solution was obtained. Slide was prepared by placing a drop of the avove solution on a clean glass slide and covered with a cover slip. The globules were focused under 45X and the size of the globules were measured using calibrated eye piece micrometer. The obtained values were

multiplied by calibration factor to get actual size of the globules. The average size of the globules were calculated by measuring the size of 25 globules in each SMEDDS formulation. [6]

Stability studies:

The short term of the unformulated itraconazole were kept in air tight vials were assessed at room temperature for 10 days. Long term stability studies were performed by placing the ready to use SEDDS in air tight vials at room temperature and these were stored. The physical stability of the preparation was determined by visually assessing the sedimentation or crystal formation in the SEDDS.

Dispersibility test:

The self emulsification of oral SMEDDS efficiency was evaluated using a standard USP XXII dissolution apparatus II. 3 ml of each formulation were added to 900ml of buffer solution (pH 1.2) at 37 ºC .[9] A standard stainless steel dissolution basket rotating at 50 rpm provide gentle agitation.[8] The *In vitro* performance of the formulation is visually evaluated applying the following graded system:

- Grade A: rapidly forming (within 1 min) nanoemusion that has a clear or bluish appearance.
- Grade B: rapidly forming, slightly less clear emulsion , having a bluish white appearance.
- Grade C: fine milky emulsion that formed in a periode of 2 min.
- Grade D: dull, greyish white emulsion having slightly oily appearance that is slow to emulsify. (more than 2 min)
- Grade E: formulation, showing either poor or minimal emulsification with large oil globule present on the surface.[7]

***Invitro* dissolution study:**

In-vitro dissolution study was carried out for all the formulations. The dialysing medium was phosphate buffer pH 1.2. One end of polymer dialysis bag was tied with thread & then 3ml of self emulsifying formulation was placed in it along with 0.5ml of dialysying medium. The other end of the bag was also secured with thread and was allowed to rotate freely in 900ml of dialysing medium and stirred continously at 50 rpm in the rotating basket at 37 ºC. Aliquots of 5ml were removed at different time intervals and diluted further. Volume of aliquots was replaced with fresh dialysing medium each time. These samples were analysed quantitatively for drug dialysis across the membrane at corresponding time by using UV- visible spectrophotometer. [8]

RESULTS AND DISCUSSION

In the present study self emulsifying drug delivery system of itraconazole was successfully prepared using benzyl alcohol and castor oil as oil phase, tween 80 as surfactant, poly ethylene glycol and ethanol as co-solvents. Various formulations and process variables that could affect the preparation and properties of self emulsifying drug delivery system were identified and optimized to get SMEDDS with smaller globule size with better process yield.

Various trials were carried out to optimize the conditions for the preparation of SMEDDS.

Different trials were carried out to optimize the amount of oils, surfactant and co-solvents.

Table 3: Trials carried out to optimize oil: surfactant: co-surfactants ratio

Formulation Trials	Drug(mg)	Castor oil(ml)	PEG400 (ml)	Ethanol (ml)	Tween 80(ml)
Trial 1	11	35.0	11.5	11.5	46.0
Trial 2	10	30.0	10.0	10.0	40.0
Trial 3	200	33.3	11.1	11.1	44.4
Trial4	100	33.3	11.1	1.11	44.4
Trial 5	500	33.3	11.1	11.1	44.4
Trial 6	100	6.0	2.3	2.30	9.2
Trial 7	100	5.0	2.0	2.0	8.0

Characterization of prepared SMEDDS

Solubility

Itraconazole showed least solubility in water, olive oil, corn oil, soya bean oil and palm oil. It showed better solubility in castor oil than other crude oils. It has maximum solubility in benzyl alcohol i.e. 159.17 mg/ml. Hence itraconazole was first dissolved completely in benzyl alcohol and were mixed with castor oil to get proper SMEDDS. Itraconazole also showed good solubility in tween 80, PEG 400 and ethanol which are used as solvent and co-solvents in the preparation of SMEDDS.

Stability studies:

The result of stability studies carried out on the optimized formulations indicated that the stability was higher for formulations containing higher concentration of oil phase. Poor stability was exhibited by those formulations with minimum amount of castor oil. From the study F7 showed more stability than F5 as the amount of castor present in it is less than the former formulation. [9]

Globule size determination:

The size of the globule size depends on the concentration of oil phase i.e. castor oil. Size of the globule ranged from 8.00-15.51 µm as shown in the table 4**.** The globule size was influenced by the amount of castor oil. It was detected that with more concentration of the castor oil, globule size

increases as seen in F6 and F7formulation. The increase in castor oil concentration leads to the increase in the viscosity which caused bigger globules during rotation with minimum change in the globule size whereas at less oil concentration, the bulk of the globule consists of solvent which rapidly evaporates resulting in breaking down of globules accounting for small globule size, but with the decrease in concentration of castor oil the formulations found to have crystal formation which leads to instability of the formulation.

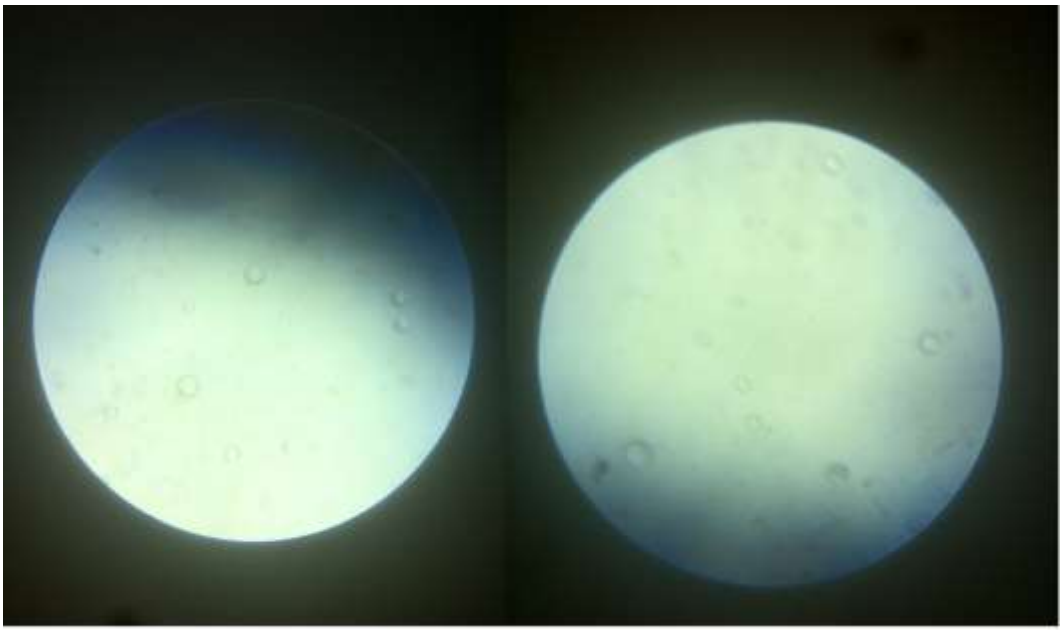

Figure 1: Picture of SMEDDS as seen under microscope

Table 4: Globule size of SMEDDS formulations of itraconazole

Formulations	Globule size (µm) Mean±SD
F1	10.600±0.25
F2	10.380±0.12
F3	11.020±0.30
F4	8.690±0.05
F5	8.004±0.04
F6	13.860±0.43
F7	15.510±0.49

` *** standard deviation, n=0.4**

Zeta Potential

Zeta potential is the difference in the potential of the dispersion medium and stationary layer of fluid linked to the dispersed particle. The importance of zeta potential is that its value can be related to the stability of globule dispersion. The zeta potential expresses the degree of repulsion between adjacent, particles that are similarly charged in the dispersion. For small particles and

molecules, a high zeta potential will confer stability, which means resistance of aggregation by the solution or dispersion [10].

SMEDDS zeta potential mainly depends on the chemical nature of the oil phase. Therefore when SMEDDS prepared from itraconazole using castor oil as oil phase, the acquired zeta potential is negative due to the existence of oil phase terminal groups existence. However, it can be stated that in most cases, zeta potential value is less than -10mV is recorded, which enables predicting good stability of SMEDDS due to high energy barrier between particles.

Table 5: Zeta potential of prepared SMEDDS

Formulations	Zeta Potential
F1	-41.4
F2	-25.6
F3	-45.7
F4	-18.7
F5	-11.5
F6	-50.5
F7	-55.6

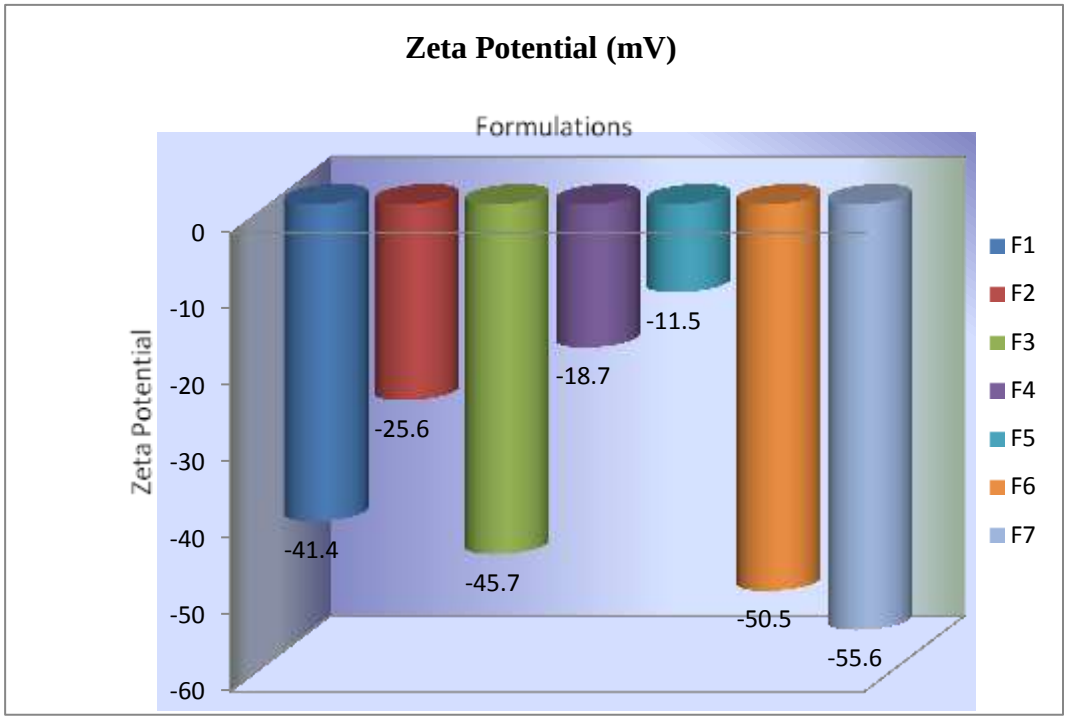

Figure 2: Zeta Potential of SMEDDS

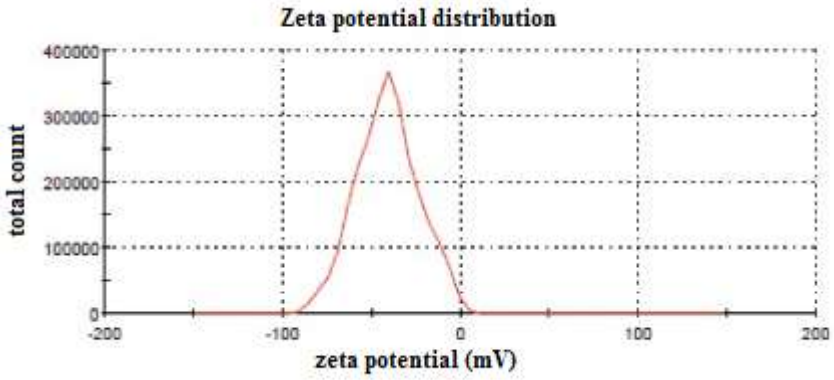

Figure 3: Zeta potential of F1

Scanning Electron Microscopy

The surface and shape characteristics of the SMEDDS were detected by SEM. The SEM photograph showed that the globules formed were roughly spherical.

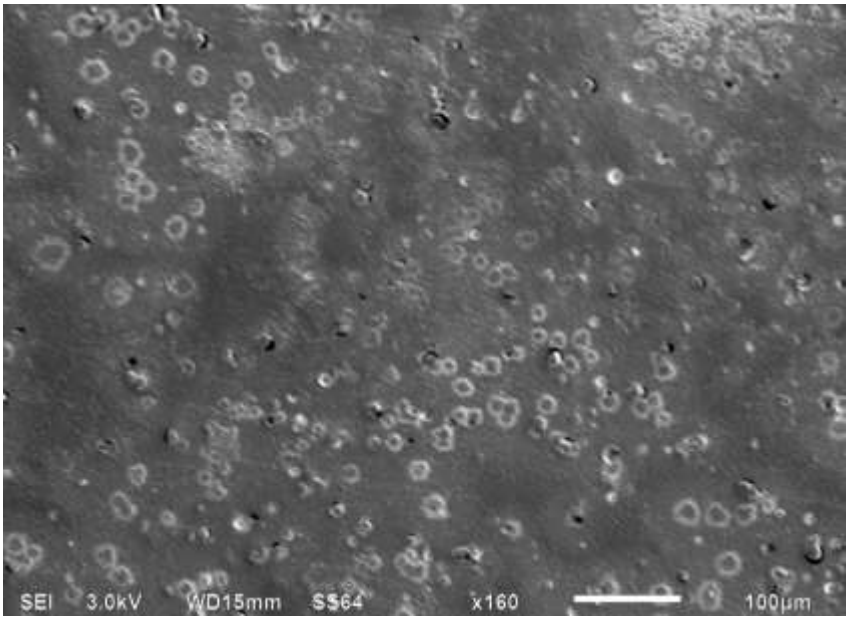

Figure 4: SEM image of globules of itraconazole

Dispersibility studies

The study was made for the identification of efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time. The emulsion formed by the prepared SMEDDS formulations was found to be an emulsion that is fine and milky which is formed in about 2 minutes at room temperature. [8]

***In vitro* release studies:**

The drug release data from various formulations of itraconazole SMEDDS are given in table 6 and the increase of drug dissolution was observed with increase in amount of oil phase. The SMEDDS

formulation of F3 and F7 of itraconazole showed rapid dissolution where more than 60% of the itraconazole was released within 15 minutes due to high concentration of oil phase. The SMEDDS formulations F2 and F4 of itraconazole showed slow release where less than 50% of itraconazole was released within 20 minutes. The formulations F5 and F6 of itraconazole showed slow release where 40-70% of itraconazole was released in 30 minutes. The SMEDDS formulation F1 was the slowest where less than 50% of itraconazole was released in 30 minutes and F7 showed highest drug release i.e. 98% of the drug was released at the end of 2 hours. Hence it can be concluded that as the drug to oil phase ratio increases, the extend of drug releases also increases.

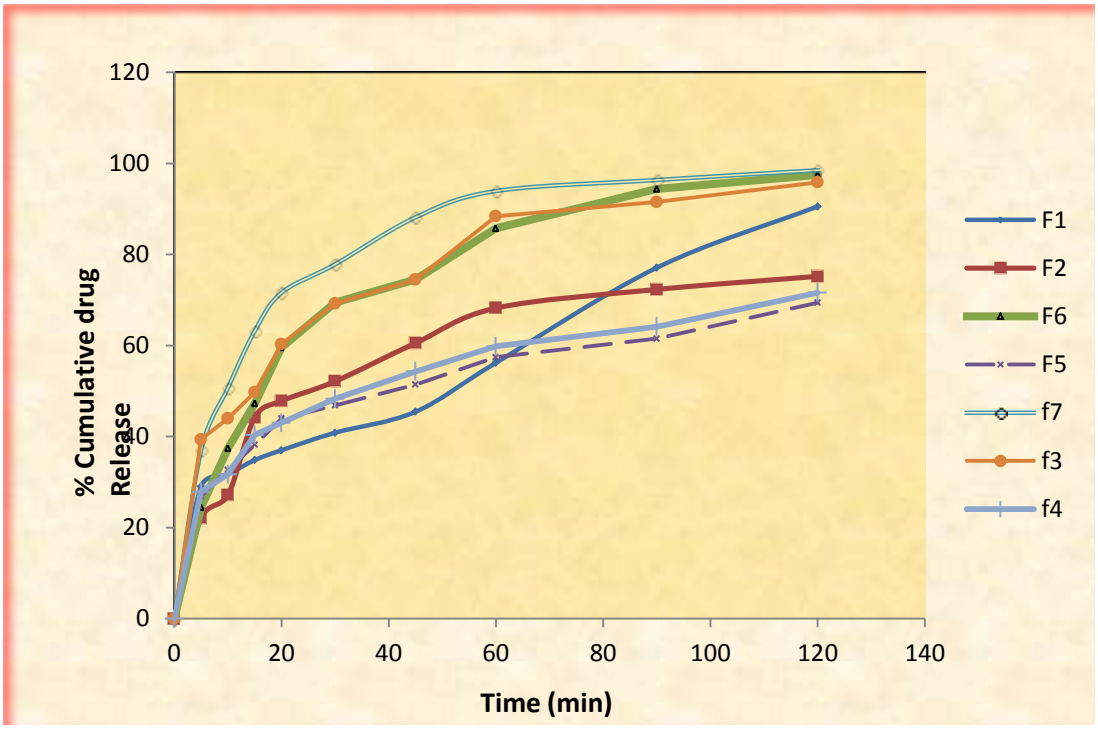

Figure 5: Graph showing the *In vitro* release profile of SMEDDS

CONCLUSION

From the results of the experimental work carried out, it can be concluded that the prepared self micro emulsifying drug delivery system can offer a promising delivery for poorly water soluble drugs. It is an efficacious system which can help in enhancing solubility of poorly water soluble drug by incorporating in the form of SMEDDS and thus can help in increasing the bioavailability.

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